

REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and arguments set forth is respectfully requested.

Claims 1-8 and 10-14 are pending and under consideration. Claim 9 has been canceled in this amendment. Claim 1 has been amended as explained below. No new matter has been added as a result of these amendments.

Rejection of Claims 1, 2 and 4-13 Under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 2 and 4-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner asserts that Applicants have not set forth a representative number of species of a genus that embraces a plethora of proteins that can be regarded as mutant proteins derived from the wild-type human Bcl-2 protein.

Applicants respectfully traverse this rejection. Applicants' arguments in the previous Response are incorporated herein.

The USPTO Written Description Guidelines (*Federal Register*, Vol. 66, No. 4, 2001) states that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (emphasis added)." *Id.* at page 1106.

As pointed out to the Examiner in the previous Amendment, the specification discloses not only the size range and make-up of the replacement sequence of a protein derived from a wild-type human Bcl-2 protein but also the size range of the mutant proteins (page 7, line 31 to page 8, line 1). The size range and make-up of the replacement sequence is at least two acidic amino acids (page 7, lines 15-20). This replacement sequence allows the protein to function with a lower isoelectric point compared to that of the wild-type Bcl-2 protein. This property allows them to function in X-ray crystallography and NMR studies as well as in assays to identify candidate compounds which block the ability of Bcl-2 to inhibit programmed cell death (pages 5-6, bridging paragraph). The specific make-up of the wild-type Bcl-2 proteins (SEQ ID NOS: 3-5) are also disclosed in the specification.

Therefore, Applicants submit that the specification discloses relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1, 2 and 4-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejection of Claims 1, 2 and 4-13 Under 35 U.S.C. § 112, First Paragraph –
Enablement

Claims 1, 2 and 4-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner maintains the rejection made in the previous Office Action. The Examiner further states that 1) Applicants have not provided sufficient guidance enabling the effective implementation of the broadly claimed mutant proteins in screening assays to identify compounds useful as anti-cancer agents for treating disorders associated with cancer and other diseases caused by the impairment of the apoptotic process, 2) Applicants have not provided sufficient evidence revealing a manageable pool of mutant proteins in which to implement in the assays discussed in the specification, 3) the specification does not provide sufficient guidance on how to make these specific mutant proteins, and 4) the broadly claimed proteins would be cumbersome to make and use in a manner reasonably correlated to the applications set forth in the specification.

Applicants respectfully traverse this rejection. Applicants' arguments in the previous Amendment are incorporated herein.

First, as shown above with respect to the adequate written description of the claimed mutant proteins, the specification provides detailed information regarding the replacement of the amino acids in the flexible loop of the wild-type human Bcl-2 protein.

The method of preparing these mutant proteins is described in the specification as based on techniques known in the art, such as by recombinant DNA techniques and purified by a number of chromatographic procedures (page 9, line 26 to page 12, line 14 and Example 1).

The specification teaches that these proteins can be used in screening assays (page 10, line 9 to page 12, line 1 and Example 2). The screening assays identify candidate compounds that are capable of binding to the mutant proteins of the present invention and thus inhibit programmed cell death. One such assay focuses on the ability or inability of candidate compounds to bind to the mutant proteins of the present invention and displace a labeled probe molecule such as a peptide. Another such assay is the competitive binding assay, where the candidate compound can compete with a labeled analyte for

specific binding to sites on a binding agent bound to a solid surface. Details and an example of a competitive binding assay are described in the specification on page 11, line 12 to page 12, line 29. However, Applicants submit that the particulars of these assays are known to one skilled in the art.

Finally, Applicants respectfully submit that although the number of mutant proteins encompassed by the claims can be large and it can be cumbersome to make them all, 35 U.S.C. § 101 does not require Applicants to claim only a “manageable pool” of mutant proteins in order to make use of the invention. Additionally, what is the number of mutant proteins the Examiner considers as to fall within a “manageable pool”?

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1, 2 and 4-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Rejection of Claims 1-13 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner asserts that the recitation “flexible loop” in claims 1, 2 and 9 is vague and indefinite. The Examiner suggests defining the loop by the amino acid residues and/or juxtaposition. Accordingly, the Examiner states that “at least a portion of a flexible loop” in claim 2 is also vague and indefinite.

Applicants respectfully traverse this rejection. Applicants’ arguments in the previous Amendment are incorporated herein.

However, in an effort to expedite prosecution of the instant application, claim 1 has been amended to further clarify the flexible loop by incorporating the subject matter of claim 9 which provides the exact amino acid position of the flexible loop from a human Bcl-2 protein. Applicants have also amended claim 1

by reciting “at least a portion of a flexible loop” in order to clarify the replacement amino acid sequence.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection of Claims 1-8 and 10-13 Under 35 U.S.C. § 102(e) – Bennett

Claims 1-8 and 10-13 are rejected under 35 U.S.C. § 102(e), as being anticipated by Bennett *et al.*, U.S. Patent No. 6,214,986 (herein “Bennett”).

Specifically, the Examiner maintains the rejection made in the previous Office Action. The Examiner states that the broad language of the claims reads on Bennett’s SEQ ID NO: 2.

Applicants respectfully traverse this rejection. Applicants arguments made in the previous Amendment are incorporated herein. Applicants would like to respectfully explain the terms and language of the claims in connection to the present invention.

First, claim 1 recites “A mutant protein derived from a wild-type human Bcl-2 protein”. A wild-type human Bcl-2 protein is defined in the specification on page 6, line 27 to page 7, line 7. Here, the specification clearly states that the wild-type human Bcl-2 is any one of the three Bcl-2 isoforms, i.e., the proteins shown in SEQ ID NOS: 3-5.

In contrast, a “wild-type human Bcl-X_L protein” is defined in the specification on page 7, lines 8-9 as the protein shown in SEQ ID NO: 6.

Bennett’s SEQ ID NO: 2 is the wild-type human Bcl-X_L protein, or a major portion of the wild-type human Bcl-X_L protein. Therefore, Bennett’s SEQ ID NO: 2 cannot read on the mutant protein as claimed in claim 1.

Thus, any amino acid sequence comparison of the prior art should be with the instant SEQ ID NOS: 3-5 and not SEQ ID NO: 6.

Applicants further submit that claim 1 has been amended to further describe the flexible loop such that the mutant protein of the instant claim 1 cannot read on Bennett's SEQ ID NO: 2.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1-8 and 10-13 under 35 U.S.C. § 102(e), as being anticipated by Bennett *et al.*, U.S. Patent No. 6,214,986.

Rejection of Claims 1-8 and 10-13 Under 35 U.S.C. § 102(b) – Thompson, Boise and Muchmore

Claims 1-8 and 10-13 are rejected under 35 U.S.C. § 102(b), as being anticipated by Thompson *et al.*, U.S. Patent No. 5,646,008 (herein “Thompson”), Boise *et al.*, Cell 74: 597-608, 1993 (herein “Boise”) or Muchmore *et al.*, Nature 381: 335-341, 1996 (herein “Muchmore”).

Specifically, the Examiner maintains the rejections made in the previous Office Action. The Examiner states that the broad language of the claims reads on the amino acid sequences disclosed in Thompson, Boise or Muchmore.

Applicants respectfully traverse these rejections. Applicants’ arguments made in the previous Amendment are incorporated herein.

The Examiner interprets the claims and applies the rejections in a similar manner as in rejection using Bennett above. Applicants submit that the Thompson, Boise and Muchmore references are deficient in a similar manner as Bennett. Applicants’ arguments above with respect to the rejection using Bennett are incorporated herein.

The claims cannot read on the amino acid sequences disclosed by Thompson, Boise and Muchmore, especially in view of the amendment to claim 1.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1-8 and 10-13 under 35 U.S.C. § 102(b), as being anticipated by Thompson *et al.*, U.S. Patent No. 5,646,008, Boise *et al.*, Cell 74: 597-608, 1993 or Muchmore *et al.*, Nature 381: 335-341, 1996

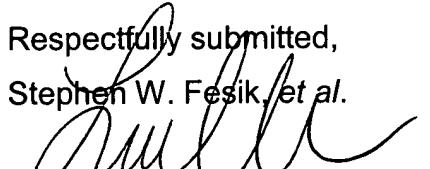
CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 112 and 102. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, he/she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,
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